On page 59, in Table 5, after "MB 1650" please insert --(SEQ ID NO: 32)--; after "MB 1651" please insert --(SEQ ID NO: 33)--; after "MB 1653" please insert --(SEQ ID NO: 34)--; and after "MB 1654" please insert --(SEQ ID NO: 35)--.

IN THE CLAIMS:

Kindly amend the following claims:

9. (Amended) The anti-human CD23 monoclonal antibody of Claim 1, wherein said antibody is selected from antibodies having a binding affinity ranging from 0.01 nM to 1000 nM.

12. (Amended) The anti-human CD23 antibody of Claim 1, wherein the light chain variable domains are derived from [5E8, 6G5 or 2C8] antibodies having SEQ ID NOs 1 and 3, and the heavy chain variable domains are derived from antibodies having SEQ ID NOs 2 and 4.

13. (Amended) The anti-human CD23 antibody of Claim 1, which is capable of inhibiting the binding of a monoclonal anti-human CD23 antibody [5E8 or 6G5] to CD23, wherein the antibody whose binding to CD23 is inhibited is selected from those having light chain variable domains selected from the group consisting of SEQ ID NOs 1 and 3, and those having heavy chain variable domains selected from the group consisting of SEQ ID NOs 2 and 4.

25. (Amended) The anti-human CD23 antibody of Claim 12, which is capable of inhibiting the binding of a monoclonal anti-human CD23 antibody [5E8] to CD23, wherein the antibody whose binding to CD23 is inhibited has a light chain variable domain having SEQ ID NO 3 or a heavy chain variable domain having SEQ ID NO 4.

Kindly add the following new claims:

--40. (New) An anti-human CD23 monoclonal antibody comprising either a human gamma-1 or a human gamma-3 constant region wherein said antibody inhibits IgE expression.

41. (New) A pharmaceutical composition containing an anti-human antibody according to claim 40.--

REMARKS

This amendment is responsive to the Office Action dated September 28, 1999. Entry of the foregoing and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 CFR §1.112, are respectfully requested.

At the outset, Applicants note that the application has been amended as proposed above. In particular, the specification has been amended to indicate the SEQ ID NO of each disclosed sequence as requested in the Office Action. Claim 9 has been amended to clarify the claim language as requested in the Office Action. And claims 12, 13 and 25 have been amended in order to define the recited antibodies by their SEQ ID NOs as also suggested in

the Office Action. The recited sequences are found on pages 44-55 of the specification. Finally, new claims 40 and 41 have been added. Claim 40 is essentially a combination between claims 1 and 3, and claim 41 is dependent on claim 40 in the same manner as claim 16 is dependent on claim 3. No new matter has been added.

Turning now to the Office Action, in section 3 on page 2 of the Action, the Examiner requires applicants to amend the specification to refer to appropriate SEQ ID NOs for all disclosed sequences. The Examiner indicates parenthetically that one such disclosed but unlabeled sequence appears at page 9, line 10. Applicants respectfully submit that no sequence was found at this point in the specification, but that applicant reviewed the specification and inserted SEQ ID NOs for all disclosed sequences identified. Accordingly, the requirement should be satisfied.

Next, claims 12, 13 and 25 were rejected under 35 U.S.C. § 112, first paragraph because they recite specific antibodies 5E8, 6G5 and 2C8, and no deposit information was provided for these antibodies in the specification. Applicants respectfully submit that the claims have been amended above to delete reference to 2C8 and define 5E8 and 6G5 according to SEQ ID NO. As the Examiner indicated that reference to specific variable region SEQ ID NOs would also overcome the rejection (see page 3 of the Action), the rejection appears to be rendered moot.

Claims 9, 12, 13, 22 and 25 were next rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. In particular, claims 9 and 22 (by virtue of its dependency on claim 9) were said to be indefinite because it was allegedly unclear how a single antibody as recited could have a range of binding affinities. Claim 9 has been

amended above to indicate that the claimed antibody is selected from a population of antibodies having a range of different binding affinities. Accordingly, the rejection pertaining to claims 9 and 22 has been rendered moot.

Claims 12, 13 and 25 were rejected for indefiniteness due to the failure to recite deposit information. Because the claims have been amended to refer to the appropriate SEQ ID NOs as discussed above, this rejection is also moot. Withdrawal of all rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

Next, claims 1, 3, 4, 6-8, 14, 16, 17, 19, 20 and 21 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Wakai et al. as purportedly evidenced by Paul et al. and D'Ambrosio et al. The Examiner believes that Wakai is applicable because it discloses murine anti-human CD23 monoclonal antibodies that bind to human Fc receptors and are of the IgG1 isotype. Applicants respectfully traverse the rejection.

Firstly, Applicants respectfully submit that Wakai does not teach an antibody that binds to human Fc receptors as required by the claim 1, because Wakai teaches murine anti-human CD23 antibodies. Such antibodies would bind to murine Fc receptors, not human. Moreover, claim 3 is directed to an anti-human CD23 monoclonal antibody that comprises either a human gamma-1 or human gamma-3 constant region. Because the reference teaches a murine anti-human CD23 antibody by the Examiner's own account (Office Action page 4), which by necessity contains murine constant regions, at the very least the reference is wholly inappropriate as § 102 art against original claim 3.

In this regard, Applicants note that new claim 40 has been added which combines the limitations of original claims 1 and 3. Thus, even if it could be argued that an antibody

having a murine IgG1 constant domain might bind to human Fc receptors, the reference does not qualify as § 102 art against new claim 40 (and claim 41 dependent thereon), because claim 40, like claim 3, requires that the antibody have a human constant region domain. Nevertheless, Applicants emphasize that a murine IgG1 antibody would not be expected to bind to a human Fc receptor in the same manner as a human IgG1 antibody. Indeed, according to the attached excerpt from Paul's Fundamental Immunology, murine IgG1 antibodies have certain characteristics in common with human IgG4 antibodies, *which do not inhibit IL4-induced IgE expression.* Furthermore, Paul cautions against assuming "parallels in the regulation and function of 'analogous' isotypes in the two species [as being] misleading." Also attached, please find a chart on page 83 of Therapeutic Immunology (1995) 2:72-94, reviewing the Fc effector functions of human IgG1, human IgG3 and mouse IgG1 which clearly indicates that mouse gamma 1, unlike human gamma 1, does not bind to FcγRI.

Likewise, claim 4 is directed to an antibody that comprises a rodent antigen binding portion. According to the Examiner, Wakai discloses an anti-human antibody, i.e., binds to human CD23. Given that this antibody is a murine antibody that was likely isolated by immunizing mice with human CD23 or cells expressing the same, it would not be self-evident, and indeed would not be expected, that the antibody of Wakai would recognize murine or rodent CD23 as well. According to the theory of positive/ negative selection during thymus "education," animals are generally not expected to produce antibodies that bind to self epitopes. Thus, it is not clear how Wakai can be classified as § 102 art against claim 4.

The Federal Circuit has held that "[t]o be anticipating, a reference must disclose each and every element of the claimed invention." SSIH Equipment v. U.S. International Trade Comm., 218 USPQ 678, 688 (Fed. Cir. 1983). Indeed, the court has stressed that "a party asserting that a patent claim is anticipated must demonstrate among other things identity of invention." Kalman v. Kimberly Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983), cert. denied 224 USPQ 520 (1984); Tyler Refrigeration v. Kysor Industrial Corp., 227 USPQ 845, 846 (Fed. Cir. 1985) (with emphasis). Therefore, "[i]t is axiomatic that anticipation of a claim under § 102 can be found only if the prior art reference discloses every element of the claim." In re King, 231 USPQ 136, 138 (Fed. Cir. 1986). Wakai is therefore not appropriate prior art because it does not disclose an antibody that binds to human Fc receptors having either a human constant region or a rodent antigen binding domain. Accordingly, withdrawal of the § 102 rejection based on Wakai et al. as evidenced by Paul and D'Ambrosio is respectfully requested.

Claims 1, 3, 4, 6, 14, 16, 17 and 19 were also rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Saxon et al. as evidenced by Paul et al. and D'Ambrosio et al. Essentially, the Examiner provides the same reasoning as for Wakai, again stating that the reference teaches murine anti-human antibodies of the IgG1 isotype that meet the limitations of the claimed invention. Applicants, again, respectfully traverse the rejection.

At the outset, Applicants note that the reference does teach murine anti-human antibodies (although this is not specifically stated in the section describing the antibodies at the top of column 1 on page 4001). Indeed, according to the flow cytometry methods section (fourth paragraph, col. 1, page 4001), the primary antibodies were detected using

goat anti-mouse antibodies, i.e., goat antibodies that bind to murine constant regions, therefore, the primary antibodies of the reference were indeed murine anti-human antibodies as alleged in the Office Action.

Given that the disclosed antibodies were in fact murine antibodies, they would not have human constant regions as required by claims 3 and 40 and as argued above for the Wakai reference, and they would not bind to human Fc receptors as required by claim 1. Accordingly, Saxon is not appropriate § 102 art against the original claims or as applied to new claims 40 and 41 either. Reconsideration and withdrawal of the rejection is respectfully requested.

Finally, claims 1-11 and 13-25 were rejected under 35 U.S.C. § 103 as being allegedly unpatentable over the combination of Wakai and Saxon as evidenced by Paul and D'Ambrosio, in view of Newman et al. and Queen et al. Essentially, it is the Examiner's opinion that, although Wakai and Saxon do not teach antibodies that are primatized or humanized, and do not teach antibodies having the specific binding affinities recited in the claims, that such would be obvious in view of Newman and Queen. Wakai and Saxon are again relied upon for allegedly teaching murine anti-human CD23 antibodies of the IgG1 isotype that bind to human Fc receptors and inhibit IL4-induced IgE expression by B cells *in vitro*. Although the Examiner does not discuss in this rejection the ability of the disclosed antibodies to inhibit such IgE expression *in vivo*, it is apparently the Examiner's opinion as evidenced by the § 102 rejection based on Wakai set forth on page 4 that such *in vivo* activity would be "inherent" in the disclosed antibodies because they allegedly have this activity *in vitro*. Applicants respectfully traverse the rejection.

Firstly, Applicants again note that neither Wakai nor Saxon teach antibodies that meet the limitations of the claimed invention, because the antibodies of Wakai and Saxon do not bind to human Fc receptors, nor do they have human gamma-1 or gamma-3 constant domains, because the antibodies disclosed in these references are murine antibodies. Thus, it is not clear why the Examiner relies on Paul et al. in order to emphasize that the PBMC's used in Wakai or Saxon express FcgR, because the antibodies disclosed in these references would not bind to such Fc receptors even if they were present on the cells. The references use PBM cells to stimulate IgE expression by B cells, and use the disclosed antibodies to allegedly bind to CD23 on those cells. Nowhere do the references state that the disclosed antibodies bind to human Fc receptors (and indeed, one would not expect them to because they are murine antibodies with murine constant regions).

Furthermore, the Examiner's reliance on Newman et al. appears to be misplaced. The Examiner argues that it would be obvious to humanize the antibodies of Wakai or Saxon because Newman et al. teaches that humanized antibodies are advantageous in that these antibodies do not suffer from immunogenicity and "*they lack effector functions with human cells*" (with emphasis, see Office Action, page 6). Yet, the crux of applicant's invention lies in the observation that the effector functions of a human gamma-1 constant region (or a human gamma-3 constant region) are important to the ability of anti-CD23 antibodies to inhibit IL4-induced IgE expression. Given that applicants have discovered that only particular human constant regions will work in the claimed antibodies presumedly by virtue of their effector functions, it is not seen how Newman et al. provides the

motivation to produce applicants' particular claimed antibodies given that Newman emphasizes a lack of effector function, not a consideration thereof.

Even if one were truly motivated by Newman to produce humanized antibodies, one would have no motivation to produce gamma-1 antibodies over, for example, gamma-4 antibodies if the only concern were immunogenicity. In fact, if one were concerned about immunogenicity, why not produce Fab fragments having only the antigen binding domain? According to the Examiner's reasoning, the particular antibodies of the present invention would be no more obvious than a gamma-4 antibody or a Fab fragment, neither of which work according to Applicants' findings. Indeed, "[v]irtually all inventions are combinations and virtually all are combinations of old elements. [The task] is to determine what the prior art would have suggested to one of ordinary skill in that art." Environmental Designs, Ltd. v. Union Oil Co. of California, 218 USPQ 865, 870 (Fed. Cir. 1983) (with emphasis). The prior art certainly did not suggest that human gamma-1 and gamma-3 constant region domains in particular would play a role in IL4-induced IgE expression.

Thus, Newman et al. fails to provide the motivation to produce the particular antibodies of the present invention, because Newman et al. does not disclose the importance of the human constant region domain. Likewise, Queen fails to make up for this missing disclosure, because Queen was only relied upon for the teaching of the range of binding affinities. In the absence of such disclosure of the requisite motivation, one of ordinary skill in the art would not be able to reproducibly achieve *in vivo* inhibition of IL4-induced IgE expression as achieved by applicants with the anti-CD23 antibodies of the present invention. Indeed, as reported on page 14 of the instant specification, although Fc effector

functions are sometimes significant to the therapeutic activity of antibodies, this was surprising in the context of anti-CD23 antibodies because it had not been previously reported. In fact, the prior art at the time suggested otherwise.

"[N]o matter what a reference teaches, it could not have rendered obvious [the invention] unless said hypothetical person [of the art] would have considered it." Ex Parte Murphy v. Burford, 217 USPQ 479, 482 (PTO Bd. & App 1982). Indeed, "there must be a reason apparent at the time the invention was made to the person of ordinary skill in the art for applying the teachings at hand, or the use of the teaching as evidence of obviousness will entail prohibited hindsight." Id. Because the prior art at the time of the present invention in fact suggested that effector function was not important to the ability of anti-CD23 antibodies to inhibit IL4-induced IgE expression, the skilled artisan would have never been motivated to engineer anti-CD23 antibodies with particular constant region domains.

Finally, Applicants respectfully submit that the Examiner makes quite a theoretical leap by arguing that something that works *in vitro* would "inherently" work *in vivo*. The Patent and Trademark Office itself has long-adhered to the argument that the complexity of *in vivo* systems often leads to unexpected results that would not be self-evident based on *in vitro* data alone. It seems only fair that the Office recognize such added complexity when considering the non-obviousness of the present invention, particularly when the alleged prior art not only reports solely *in vitro* data, but also fails to point to the crucial aspect of the antibodies, that is, that they must have a gamma-1 or gamma-3 constant region, as claimed in the present invention.

In view of all the remarks above, Applicants respectfully submit that the rejection under § 103 based on Wakai or Saxon in view of Newman and Queen is not appropriately applied against the present claims. Reconsideration and withdrawal is respectfully requested.

Applicants respectfully submit that the above amendments and remarks constitute a complete response to the Office Action dated September 28, 1999. A Notice of Allowance appears to be next in order. If there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned at her earliest convenience.

Respectfully submitted,

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